77. (New) The pharmaceutical composition according to claims 72 or 73 wherein said LHRH is the amino acid sequence of SEQ ID NO:4.

78. (New) A composition for use in eliciting an effective immune response to LHRH said composition comprising a LHRH- conjugated to diphtheria toxoid and adsorbed to an ionic polysaccharide wherein said LHRH is an amino acid sequence of at least 5 contiguous amino acids of the C-terminal end of SEQ ID NO:1.

79. (New) A pharmaceutical composition comprising a LHRH- conjugated to diphtheria toxoid and adsorbed to an ionic polysaccharide together with one or more pharmaceutically acceptable carriers and/or diluents, wherein said LHRH is an amino acid sequence of at least 5 contiguous amino acids of the C-terminal end of SEQ ID NO:1.

80. (New) The composition of claim 1, wherein said LHRH derivative comprises spacers introduced at the N-terminus.

81. (New) The composition of claim 5, wherein said LHRH derivative comprises spacers introduced at the N-terminus.

82. (New) The composition of claim 1, wherein said LHRH derivative comprises at least one amino acid substitution according to table I.

83. (New) The composition of claim 5, wherein said LHRH derivative comprises at least one amino acid substitution according to table I.

REMARKS

Introduction

Receipt is acknowledged of a final office action dated December 18, 2002. In the action, the examiner rejected claims 1-8 for allegedly failing to meet the written description and enablement requirements and for obviousness reasons.

Status of the Claims

In this response, applicants amended claims 1, 3-5 and 7-8, and added new claims 62-83. Support for the amended claims 1, 3-5 and 7-8 can be found on page 1, 1st paragraph,

page 5, last paragraph, and page 6, last paragraph. Support for new claims 62-83 can be found on page 5, last paragraph, page 6, last paragraph, and page 7, table 1. Upon entry of this amendment, claims 1-8 and 62-83 will be pending. Applicants respectfully request entry of this amendment as it does not necessitate a further search and does not raise new issues. Applicant respectfully requests reconsideration of the present rejection in light of the following remarks.

35 U.S.C. § 112 1st paragraph

Rejection based on Alleged Lack of Written Description

The examiner rejected claims 1-8 allegedly for failing to meet the written description requirement. In particular, the examiner appeared to believe that "the disclosure fails to provide a representative number of species to describe the [claimed] genus" (office action at 4). Applicant respectfully disagrees.

In levying a written description rejection, an examiner has the burden of presenting by a preponderance of the evidence why a person skilled in the art would not recognize in an applicant's disclosure, a description of the invention defined by the claims. *See In re Wertheim*, 541 F.2d 257, 263 (CCPA 1976). Applicants assert that the Examiner has failed to meet her burden.

The fundamental factual inquiry regarding the adequacy of disclosure is whether the application conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the claimed invention. *See Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). To provide descriptive support, it is not necessary that the application describe the claim limitations exactly. *See e.g. In re Lukach*, 442 F.2d 967, 969 (CCPA 1971)([T]he invention claimed does not have to be described *in ipsis verbis* in order to satisfy the description requirement of § 112.) Rather, the application need only be sufficiently clear that persons of skill in the art would recognize that the Applicant had possession of the claimed invention. *See In re Wertheim*, 541 F.2d at 263. Thus, the written description requirement is satisfied when each claim limitation is supported explicitly, implicitly or inherently in the originally filed disclosure. *See* Guidelines for

Examination of Patent Applications Under the 35 U.S.C. 112 ¶1, "Written Description" Requirement, 66 Fed. Reg. 1099 (2001).

In the present case, it appears that the examiner has not appreciated that LHRH is a well defined molecule conserved across all mammals and is only 10 amino acids in length. Therefore, contrary to the examiner's assertions, the genus of LHRH compositions that comprise "an amino acid sequence of at least 5 contiguous amino acids of the C-terminal end of SEQ ID NO: 1" as recited in the claims is limited.

In addition, the specification discloses that a peptide consisting of amino acids 1 to 10, 2 to 10 or 3 to 10 of the peptide described in SEQ ID NOS:1-4 is advantageous for preparing an LHRH composition comprising diptheria toxoid and an ionic polysaccharide. *See* Application at 4, lines 11-13 and at 5, lines 21-23. Furthermore, the specification discloses that LHRH C-terminal fragments comprising at least five amino acids are suitable for use in the present invention. *See, Id.* at 1, lines 4-6. Thus, one of ordinary skill in the art would recognize that applicants had possession of a peptide consisting of an amino acid sequence from position 4 to position 10 of SEQ ID NO:1, position 5 to position 10 of SEQ ID NO:1, and position 6 to position 10 of SEQ ID NO:1, wherein the peptide or portion thereof is suitable for use in a composition that is capable of eliciting an immune response. Moreover, the 4-10, 5-10 and 6-10 forms of LHRH are well described in the art. *See*, applicant's arguments and references cited in Paper No. 18 at 5.

With regard to the LHRH derivatives recited in the claims, a skilled artisan is guided by both the specification and what was well know in the art with respect to designing and making modifications to very small peptides. For example, a LHRH derivative that comprises spacers that have been introduced at the N-terminus are described on page 22 and in example 3 of the specification. Furthermore, methods for making LHRH derivatives that comprise specific amino acid substitutions are also described in Table 1 of the instant application and are well within the purview of a skilled artisan. As such, applicant asserts that the written description requirement is satisfied.

The examiner also asserted that "there is inadequate written description about the structure associated with [the] function of *any* LHRH [that] 'comprises' a C-terminal fragment of at least five amino acids because the term 'comprises' is open-ended" and

"expands the LHRH to include additional amino acid[s] at either or both ends" (office action at 3).

In the interest of expediting prosecution, applicant amended the claims to recite "an amino acid sequence of at least 5 contiguous amino acids of the C-terminal end of SEQ ID NO: 1 or derivatives thereof." Applicant also amended the specification so that the definition of LHRH "derivatives" on page 5 no longer recites "chemical equivalents, mutants, homologues and analogues" and deleted reference to sequences which have "at least 50% similarity thereto." Accordingly, the definition of derivatives is now limited to fragments of LHRH and to amino acid substitutions, deletions and additions of a LHRH sequence.

Rejection based on Alleged Lack of Enablement

Continuing, the examiner rejected claims 1-8 allegedly for non-enablement. In particular, the examiner contended that "[t]he specification does not teach *any* LHRH fragment comprising any additional amino acids having the same functions and activity as SEQ ID NO: 1-4" (office action at 10). The examiner also cited three references which were purported to support the statement that "it is unpredictable which undisclosed LHRH...would be effective for a composition for use in eliciting [an] antibody immune response to LHRH" and that "it would require undue experimentation...to practice the claimed invention" (office action at 11).

The law, however, does not require a patent applicant to exemplify every species in a genus, in order to show enablement of that genus. *See Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991). Rather, the specification must provide sufficient guidance to allow practice of the invention without undue experimentation. Fulfillment of the requirements of §112 does not require that the skilled artisan be able to predict, with certainty, which embodiments of the claimed invention would be enabled, but need only describe procedures that can be practiced, without undue experimentation, to determine which embodiments are encompassed by the claims. *See, e.g., Wands*, 858 F.2d 731 ("Practitioners of this [monoclonal antibody] art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.").

As stated above, LHRH is not a large protein, and in fact, is essentially a simple, linear peptide of 10 amino acids that corresponds to a single epitope only, defined by 5 contiguous C-terminal amino acids of SEQ ID NO:1. Thus, only six LHRH forms comprise this genus (*i.e.*, the 1-10, 2-10, 3-10, 4-10, 5-10 and 6-10 forms). As the peptide is very small, applicants submit that the predictive difficulties raised in Ngo *et al.* are generally not applicable to the presently claimed invention. Applicants also submit that as a result of the small size of LHRH, Kuby and Abaza do not raise applicable issues in regard to the claimed LHRH compositions. Since sequence listings for each of the three out of the six LHRH forms are described in the application, applicant argues that the enablement requirement is satisfied.

With regard to the LHRH derivatives of the present invention, this term represents a defined subset of acceptable LHRH forms. Nevertheless, in the interest of expediting prosecution, applicant amended the claims to recite "an amino acid sequence of at least 5 contiguous amino acids of the C-terminal end of SEQ ID NO: 1 or derivatives thereof." "Derivatives," as recited in the claims, connotes fragments, parts, or portions from natural, synthetic or recombinant sources, including amino acid insertion, deletion or substitions.

In addition, methods for making and using a modified LHRH based on the acceptable amino acid substitutions is provided in Table 1. The specification also discloses that spacers can be introduced at the N-terminus to create an LHRH derivative, and exemplifies this teaching by providing SEQ ID NO: 4.

Moreover, methods for screening an LHRH component for immunogenicity are described in the examples. As such, (i) the small genus of LHRH forms, (ii) the specific disclosure of SEQ ID NOs 1-4, (iii) the teaching of acceptable amino acid substitutions in Table 1, and (iv) the teaching that spacer sequences can be used to modify LHRH as in SEQ ID NO: 4, clearly demonstrate that ample guidance on to make and use the LHRH compositions of the present invention. Therefore, the amount of experimentation required to practice the claimed invention would not be undue.

35 U.S.C. § 103

The examiner rejected claims 1-8 as allegedly obvious over U.S. 5,378,688 (Nett *et al.*) or Sad *et al.*, *Immunology*, 74:223-227 (1991), in view of U.S. 5,614,487 (Battersby *et al.*) or U.S. 5,403,586 (Russell-Jones *et al.*). Applicants respectfully disagree.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. And finally, the prior art references (or references when combined) must teach or suggest all the claim limitations. *See* MPEP 2142. Applicants tend that the examiner has failed to meet her burden for a showing of obviousness.

The present invention discloses compositions for use in eliciting an effective immune response to LHRH comprising a LHRH-diptheria toxoid conjugate ***adsorbed to an ionic polysaccharide***. To iterate our last response, the '688 patent does not teach an immunological or vaccine-like composition. In fact, '688 discloses the use of LHRH conjugated to a toxic compound that binds to cells expressing a receptor directed to that hormone. Upon interaction of the hormone with the receptor, the hormone-linked toxic compound destructs the cell expressing the receptor ***by virtue of the actions of the toxic compound***.

Thus, applicant respectfully asserts that ***the composition disclosed in the '688 patent is not capable of eliciting an effective immune response***. The very presence of the toxin coupled to the LHRH would arguably lead to the killing of any cell to which the LHRH is coupled and therefore prevent an immune response from being generated. Indeed, the '688 patent provides for toxin mediated destruction of any cell to which the LHRH component binds. In other words, chemical castration as described in the art is achieved by destroying cells that express GnRH receptors, and not by the induction of an immune response.

Additionally, Sad *et al.* (1991) teach away from the notion that one can develop a vaccine formulation which results in a significant proportion of an outbred population responding effectively to an LHRH conjugate subunit type vaccine. In fact, Sad show

suppression as well as some stimulation of an immune response to GnRH. This would cause one skilled in the art of vaccine formulation to expect a significant proportion of an outbred population to fail to respond or poorly respond to an LHRH conjugate subunit type vaccine, irrespective of the carrier protein and adjuvant which are used.

In the action, the examiner stated that "[t]he claimed invention in claims 1 and 6 differs from the references only by the recitation...[of an] ionic polysaccharide[,] wherein said polysaccharide is DEAE dextran" (office action at 6). While dextrans are known in the art, neither the '688 patent nor Sad provide any teaching or suggestion to include or substitute an ionic polysaccharide as described in US 5,614,487 or US 5,403,586 for alum.

Applicant submits that the examiner is relying on hindsight in making the above obviousness rejections of the cited claims under 35 U.S.C. §103(a). Applicant believes that the examiner is basing her rejections on the mere identification in the prior art of individual components of claimed limitations in the present application. The Examiner has not made particular findings as to the reason a skilled artisan, with no knowledge of the claimed invention would have selected the components for a combination in the manner claimed in the present application. See, *In Re Kotzab*, 55 U.S.P.Q.2d 1313, 1317 (CAFC, 2000).

In order to avoid an improper use of hindsight, the burden lies on the Office to show a motivation to combine references that create the case of obviousness. *In re Rouffet*, 149 F.3d 1350, 1356 (Fed. Cir. 1998). Specifically, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. *Id.* The Federal Circuit has identified three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art. *Id.* None of those possible sources of motivation are found in this case.

But even assuming, for arguments sake, that one of ordinary skill in the art would have been motivated to combine either of the primary references with the '487 patent or the '586 patent, the superior efficacy of the claimed composition would not have been predicted. As the *Corkill* court described, "[a] greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness...of the claims at issue." *In re Corkill*, 711